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Editorial

Gathering, connecting, integrating

Medicinal research is inherently an integrative one. To understand human physiology and pathophysiology, it is compulsory to investigate how organisms, organs, cells, and biomolecules carry out their chemical or physical functions. However, owing to the insurmountable limits of (ordinary) human intelligence, it is very difficult to have an integrative anticipation of the complex organism's responses, especially in precise time dependence. In fact, in most medical sciences, biomedical experiments are performed under careful designs to minimize the variables in the objects of research. This means that the results obtained in a conventional study are inherently excluding or intentionally ignoring the possibility of mutual or multilateral interactions causing continuous changes of all components.

Nevertheless, the integrative approach should be the ultimate goal of medical research. For example, integrated physiology focuses on the integrated processes that take place between the cardiovascular, respiratory, and urinary systems. Such processes enable the body to regulate fluid volume, internal temperature, pH levels, and blood pressure. How, then, can we attain our goal? Naturally, the fundamental step is gathering a variety of data obtained at different levels of complexity. However, even a huge size of data collection does not ensure the benefits of integration. Without understanding the logic and laws of interactions between the natures of data groups, the collecting behavior would simply result in the "stacking" of data. Thus, the act of connecting the dots is a fundamental issue of the integrative approach.

Then, one might say that wise connection is the essential process of integration. However, it is often overlooked that novel features can emerge by allowing mutual interactions between multitudes of connections in the whole organism or even in the single organ system. Needless to say, living conditions, environment, and lifestyle are interwoven together, influencing human diseases much more strongly than the genetic code. Some people believe that the zip code is actually shaping our genetic code through the molecular processes such as epigenetic modification.

The present volume of *Integrative Medicine Research* provides nine interesting reviews contributed by excellent researchers from various fields of medicine and sport sciences. The

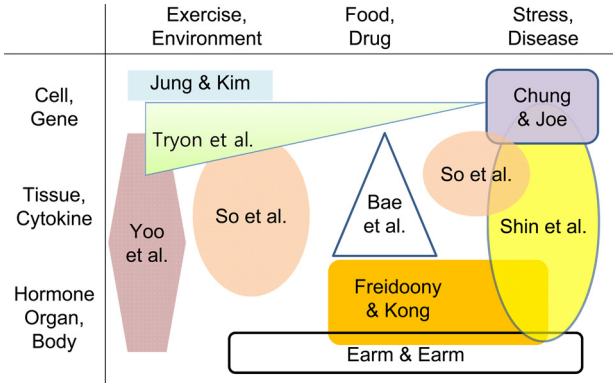

Fig. 1 – Schematic drawing of the relative positions for the articles in this special issue. The spectrum of subjects ranges from Cell & Gene to Whole Body (vertical axis) as well as from Exercise & Environment to Stress & Disease (horizontal line).

spectrum of subjects covered by these papers ranges from gene regulation to the whole body as well as from exercise training to diseases (Fig. 1). Jung and Kim summarize their previous and current discoveries as well as integrate the knowledge of transcription factors induced by exercise training, which provide the fundamental understanding of increased exercise capacity by training. By contrast, Tryon et al focus on the effect of disuse muscle atrophy. More specifically, the decline of mitochondrial number and function is summarized in an elegant manner. Such knowledge is especially important to prevent the loss of metabolic functions in the era of sedentary lifestyle and aging populations. What are the extracellular signals explaining the above changes, i.e., hormones and cytokines released from skeletal muscle during exercise? The answer to this question, so called myokine, is currently the hottest issue in exercise physiology. So et al provide details on the variety of myokines, which are the main focus of their recent studies. In common with the issue of disuse atrophy (Tryon et al), the knowledge of the exact nature of myokines would be beneficial to overcome metabolic diseases,

which is the reason their paper is located at two places in the diagram (Fig. 1).

An adequate supply of oxygen is the critical issue for multicellular organisms including humans. For terrestrial animals with lung respiration, even matching between ventilation and pulmonary blood perfusion is highly important to prevent systemic hypoxemia. The paper by Yoo et al deals with oxygen sensing by pulmonary arteries, i.e., hypoxic pulmonary vasoconstriction (HPV). There have been numerous controversies surrounding the molecular mechanisms and hormonal factors determining HPV. Their review clearly shows that such controversies arise from the level of experimental approach and the complexity of objects: from a molecule to the whole organ. Some factors that appear to be critical at the cellular level became overshadowed by other factors in organ-level studies. Therefore, this review emphasizes the importance of an integrative approach for understanding physiological phenomena such as HPV.

Many of us, although not all, are a little bit worried about the amount of coffee we drink every day. The short review by Bae et al raises an intriguing issue on the relation between coffee drinking and human health. The readers will find their answer from the information provided by Bae et al. The strategy of nutrient uptake is the fundamental issue for patients with chronic diseases. Nevertheless, this is an area where not enough attention is paid. Freidoony and Kong focus on nonalcoholic fatty liver disease, which is increasingly turning into a health issue globally. It is my hope that the general readers of this journal would realize that wise nutrition can serve as a route to an effective and individualized health care.

In addition to infection and autoimmune diseases, chronic inflammatory responses are an underlying factor in aging and metabolic diseases, which are critical current health issues. The signaling mechanisms and genetic regulations are highly complex and interwoven. Chung and Joe shed a bright light on this labyrinth and provide guidance via SIRT1, PARP-1, and -2 mediated signaling mechanisms. Zooming out from the intracellular pathways, Shin et al draw our attention to a rather unknown path to stress signals via a cardiovascular disease model. Beta adrenergic overstimulation is a popular animal disease model for heart failure. Although the selective systemic stimulation of beta receptors are rather an unlikely situation, the changes in vascular functions as well as cardiac functions would provide intriguing knowledge that can be applied to enhance our understanding of the pathophysiology of stress-related diseases.

Taken together, the papers discussed above emphasize the importance of the integrative approach for the scientific understanding of human life, which is “physiology.” Among large pharmaceutical companies nowadays, target-based drug discoveries are a big issue. There, the target often means the molecular target or a specific pathway. The problems of such a top–down or reductionist approach are well described in the elegant review by Earm and Earm. As they have concluded, “Seeing things in an integrative manner to unravel the mystery of life” should be the primary attitude to adopt not only for drug discoveries in the future but also for scientists and doctors who are part of the health care system. I hope the readers would be able to find insights as well as information in this special volume of the journal. We have gathered issues and suggestions, and I tried to connect them here. Integration depends on you.

Sung Joon Kim*
Department of Physiology, Department of Biomedical Sciences and Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea

* Department of Physiology, Department of Biomedical Sciences and Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Daehak-Ro 103, Jongro-Gu, Seoul 110-799, Korea.
E-mail address: sjoonkim@snu.ac.kr

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